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08/807,500	02/27/97	ZEICHER	M 236007

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1635	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/807,500	Applicant(s) Ziecher
	Examiner Sean McGarry	Group Art Unit 1635

☒ Responsive to communication(s) filed on *May 20, 1998* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-27* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 24-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed 5/20/98 have been fully considered but they are not fully persuasive. In view of applicant arguments and the Declaration of Dr. Marc Zeicher, filed 5/20/98 the grounds of rejection under 35 U.S.C. 112, first paragraph in regard to non-pharmaceutical composition claims have been withdrawn. Applicant has demonstrated that parvoviral vectors as claimed could be used in the expression of genes that would reduce cell proliferation or effect cell death in cell culture. However the weight of evidence provided in the declaration does not overcome the rejections of record that pertain to pharmaceutical compositions or method of treatment that include a parvoviral vector. These reasons are repeated below with further evidence for the unpredictability in the art in regard to nucleic acid therapy and reasoning for the non-enablement of the instant invention that are drawn to nucleic acid therapy.

The invention as claimed is drawn to nucleotide sequences that contain an "effector sequence." The specification defines (page 9, third and fourth full paragraphs) an "effector sequence" as a nucleotide sequence which, when expressed, encodes an "effector polypeptide"

capable of destroying or normalizing treated cells and a nucleotide sequence where, when transcribed is an antisense or ribozyme capable of destroying or normalizing treated cells. The scope of this definition includes innumerable polypeptides and antisense RNAs and ribozymes where the instant specification fails to provide guidance for one of skill in the art to effect a treatment of any cancer or infection. Claim 10 limits the "effector nucleic acid sequence" to nucleic acids that encode cytotoxic polypeptides, molecules that confer on a transfected cell sensitivity to a toxic agent, and a polypeptide capable of inhibiting tumor neoangiogenesis. These limitations do not limit the scope of the claimed invention as to be enabled. The specification prophetically suggests polypeptides that posses the above properties and gives no guidance or direction for other polypeptides that have these characteristics. There are no working examples either *in vivo* or *in vitro* for such polypeptides in a parvoviral vector that will destroy or normalize a cancerous cell or virally or bacterially infected cells.

The claimed invention is drawn to ribozyme, antisense and gene therapy. A recent review by Stull et al discloses the many problems faced by artisans in the application of these systems *in vivo* and in cell culture. Stull discloses (page 476, left column second full paragraph) "[n]ucleic acid drugs must overcome several formidable obstacles before they can be widely applied as therapeutics. These obstacles require improving the stability of polynucleotide drugs in biological systems, optimizing the affinity and efficacy of the drug without reducing its selectivity, and targeting delivering nucleic acids across cell membranes." Stull et al further disclose(page 476 last paragraph bridging to page 477) " . . . none of the modalities proposed to date can eliminate the

disease/target. Thus suppression of disease will require the continued presence of the agent until the disease is cured or the condition is eliminated . . . This makes treatment of chronic disorders such as HIV infection a difficult undertaking. An obvious solution to the persistence issue for agents that are composed of RNA is to have the patient produce their own medicine via the gene therapy route. This approach reduces the requirement for frequent administration but does not circumvent the other two issues, access and entry into the target cell." Stull further discloses in the subsequent paragraph "[i]f the target is outside the vascular system, the agent will have to extravasate. Non-gene nucleic acids drugs have molecular weights in the 3,000-10,000 Dalton range so extravasation is not a particular problem for the agent itself. However, as these drugs do not permeate into the cytoplasm of cells but are found primarily in the endosome compartment, they will most likely require some covalent modification or delivery system to mediate their efficient entry into the cytoplasm of the target cell. Numerous delivery agents have been developed to facilitate uptake of oligonucleotides in cell culture. These include attempts to modify the ionic backbone, modifications to increase hydrophobicity (e.g., attachment of cholesterol) as well as attempts to attach a targeting ligand such as biotin or a neoglycoprotein directly to the nucleic acid drug. To date these efforts have led to improved uptake but not to improved cytoplasmic delivery."

The problems disclosed by Stull et al are apparent in the *in vitro* data in Example 7(Table 1) and in Example 9 of the instant specification. Table 1 shows the Fluorescence of cells transfected with a parvovirus containing the murine B7 gene. It is apparent that less

than 1% of the 10,000 cells transfected expressed the B7 gene at any significant level. In Example 9 it appears that applicant admits that CAT expression is expressed at varying levels in different cell types which is indicative of the unpredictable nature of the art.

Dupont et al Disclose the use of an autonomous parvoviral vector for the expression of the CAT gene in transformed cells. Dupont et al disclose (page 1397 last full paragraph) "[t]his therapeutic approach implies designing a recombinant parvovirus based vector which(I) can be efficiently packaged into infectious viral particles, (ii) retain the parvoviral tropism for tumor cells, and (iii) selectively express a potent therapeutic gene such as one coding for a toxin, a prodrug, or a cytokine in order to increase the intrinsic parvoviral antineoplastic activity." The specification as filed does not provide guidance or direction or working examples for the selective expression of such "therapeutic genes" and does not provide guidance or direction for providing high titer stocks that are required for therapeutic approaches. Dupont et al further disclose (page 1404 last paragraph) that the levels of viral DNA replication and the P38-driven expression of CAT are not necessarily correlated. This disclosure is indicative of the unpredictable nature of the art. Dupont et al disclose in the last paragraph of page 1405 that because some neoplastic cells such as B lymphocytes can escape transduction, which is presumed to be due to the lack of surface receptors for the viral vector, some of the natural tumors will constitute preferential targets for transduction by MVM-based vectors, while others could prove resistant. Dupont et al then state "[v]erifying this hypothesis implies evaluating potential oncoselective transduction mediated by MVM vectors both *in vitro*, with natural cancer tumor cell lines, and *in vivo*, with animals bearing

model xenogenic or syngeneic tumor grafts." There is no guidance or direction and no examples in the specification as filed that would correlate to the oncoselective transduction of cancer cells or infected (viral or bacterial) cells with the vector of the claimed invention such that there is any destruction or normalization of any type of cancer cell or cells infected by any virus or bacteria *in vitro* or *in vivo*.

Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, therby interfering in the disease process" (page376); (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379). Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense and ribozyme art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug

design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Because of the lack of guidance, the unpredictability of the nucleic acid therapy art, and lack of working examples in the specification as filed, the invention as claimed is not enabled. One of skill in the art would have been led to perform undue experimentation to practice the invention as claimed. The undue experimentation would include: trial and error experimentation to determine what polypeptides, antisense RNAs, and ribozymes would effect the normalization or destruction of cancer cells or infected cells; overcoming the obstacles of gene therapy, antisense, and ribozyme systems as disclosed by the above references; determining a method for the production of high titre stocks of a parvoviral vector; to determine the level at which a specific gene will be expressed in a given cell type with any given promoter that would effect a therapy; and determining what promoter would function in a parvoviral vector to initiate appropriate levels of expression of a desired nucleic acid sequence product so as to destroy or normalize cancer cells or infected cells. Furthermore the invention is not enabled due to the unpredictability in the art, as is evidenced by the varying levels of expression of gene products in various transformed cell types and the lack of correlation in expression levels and vector replication in various transformed cell types disclosed by Dupont et al.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

> has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

3. Claims 1-7, 9-12, 14-17, 21, and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Maxwell et al [US Patent No. 5,585,254].

Maxwell et al disclose autonomous Parvoviral gene delivery vehicles and expression vectors. The autonomous vectors include LuIII, MVMi, MVMp, and H1, for example. These vectors are disclosed to express compounds such as antisense RNA, ribozymes, RNA-based drugs, and cytotoxic proteins. It is disclosed that 90 percent of an autonomous parvovirus can be modified tp produce a desired heterologous vector and NS and VP gene can *optionally* be kept in a vector for desired characteristics. It is disclosed that any cis acting nucleic acid sequence from which polymerase can be used to initiate transcription and "response element can be included in the vector. It is disclosed that control elements and coding regions can be combined in a variety of ways (see column 10, last full paragraph, for example). It is further disclosed that a "cell-selective response element can be include and include, for example, elastase I enhances, and HIV response elements such as TAR. It is also disclosed that virus particles can be produced that selectively target desired cell types (see column 18, for example).

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 8, 13, and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maxwell et al [US Patent 5,585,254].

The instant invention is drawn to a parvoviral vectors that include; 1) an enhancer nucleotide sequence specific for CMV and includes a ribozyme directed to CMV, 2) an LTR sequence of HIV that lacks the enhancer NF-Kappa B and/or NRE, 3) a sequence encoding interferon-α, interferon-β, or PAF-4. 4) the specific promoters/enhances recited in claim 21.

Maxwell et al have taught autonomous Parvoviral gene delivery vehicles and expression vectors. The autonomous vectors include LuIII, MVMi, MVMp, and H1, for example. These vectors express compounds such as antisense RNA, ribozymes, RNA-based drugs, and cytotoxic proteins. It has been taught that 90 percent of an autonomous parvovirus can be modified tp produce a desired heterologous vector and NS and VP gene can *optionally* be kept in a vector for desired characteristics. It has been taught that any cis acting nucleic acid sequence from which polymerase can be used to initiate transcription and "response element" can be included in the vector. It has been taught that control elements and coding regions can be combined in a variety of ways (see column 10, last full paragraph, for example). Further it has been taught that a "cell-selective response element" can be include and include, for example, elastase I enhancers, and HIV response elements such as TAR. It is also disclosed that virus particles can be produced that selectively target desired cell types (see column 18, for example). Maxwell et al have not specifically taught the specific limitations listed above. However, the specific limitations recited in

the instantly rejected claims do not define the instant invention over the prior art. Maxwell et al have taught the general concepts in the construction of parvoviral vectors where the specific limitations are embraced within those teachings. Maxwell have provided several examples for specific embodiments of expression products such as antisense RNA, ribozymes, RNA-based drugs, and cytotoxic proteins and further has taught that control elements and coding regions can be combined in a variety of ways where promoters are suggested and exemplified. The instant limitations would be a matter of choice in the choosing of specific promoters, enhancers and desired expression products. The limitations instantly recited are members of the promoter, enhancers and expression products that could have been used in the parvoviral vectors described by Maxwell et al, where the instant limitations represent known promoters, enhancers, expression products and "response elements". There would have been an expectation of their successful application since Maxwell et al have described correlative limitations in their parvoviral vectors.

The invention as a whole would therefore have been *prima facie* obvious to one of ordinary skill in that art at the time the invention was made.

6. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1635.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean McGarry whose telephone number is (703) 305-7028.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. Papers should be faxed to Art Unit 1635 via the PTO Technology Center Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see C.F.R. 1.6(d)). The Art Unit 1635 FAX number is (703) 308-4242 or (703) 305-3014. NOTE: If Applicant **does** submit a paper by Fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

NANCY DEGEN
PRIMARY EXAMINER

Sean McGarry

August 12, 1998